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REMARKS

I. Status Summary

Claims 1-124 were filed with the instant application. Of these, claims 1-22 were cancelled by way of a March 18, 2004 Preliminary Amendment. Claims 41-124 have been withdrawn from consideration pursuant to the October 4, 2005 Restriction Requirement, and are also cancelled herein. Applicants hereby reserve the right to file one or more divisional patent applications directed to the unelected subject matter. Claims 23-40 remain pending in the present application.

Claims 23 and 38 have been amended herein. Support for the amendments can be found throughout the specification as filed, including particularly page 15, lines 2-7; page 24, lines 25-32; page 48, lines 22-29; page 52, lines 3-5; and page 57, line 16, through page 58, line 24. No new matter has been added.

Claim 36 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter to which applicant regards as the invention.

Claims 23-36 and 38-40 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Rogona *et al.* (*J Mol Biology*, (1999) **293**:953; hereinafter referred to as "Rogona *et al.*") in view of Smith *et al.* (*Biochemistry*, (1998) **63**:285; hereinafter referred to as "Smith *et al.*") in combination with Ehring *et al.* (*Analytical Biochem*, (1999) **267**:252; hereinafter referred to as "Ehring *et al.*").

Claim 7 presently stands rejected under 35 U.S.C. §103(a) as being unpatentable over Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* and further in view of Villaneuva *et al.* (*Fed. Euro. Biochem Soc*, (2000) **472**:27; hereinafter referred to as "Villaneuva *et al.*").

II. Response to the 35 U.S.C. § 112, Second Paragraph, Rejection

Claim 38 presently stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention. Particularly, the Patent Office asserts that with respect to claim 38, step (c), it is unclear what is meant by the phrase "change in position."

After careful review of the rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Applicants respectfully submit that claim 38, step (c), has been amended herein to recite, "identifying a change in the transition midpoint of the first denaturation curve relative to the transition midpoint of the second denaturation curve, wherein a difference in the transition midpoints of the first and second denaturation curves is indicative of a binding event involving the test ligand and the test protein." Particularly, the amendment to claim 38 has been made in an attempt to clarify the asserted indefiniteness by pointing out that the change in position of the first and second denaturation curves refers to a change in the transition midpoint of the first and second denaturation curves, respectively. Support for the amendment can be found throughout the specification as filed, including particularly at page 51, line 31, through page 52, line 5, of the patent application. No new matter has been added.

Accordingly, applicants contend that the 35 U.S.C. §112, second paragraph, rejection of claim 38 has been addressed, and request that the instant rejection be withdrawn at this time. A Notice of Allowance is also respectfully requested.

III. Response to the 35 U.S.C. §103(a) Rejections

III.A. Response to the Rejection of Claims 23-36 and 38-40 Based on Rogona *et al.* in view of Smith *et al.* in Combination with Ehring *et al.*

The Patent Office asserts that Rogona *et al.* teach each element of independent claim 23, except a binding event and using mass spectrometry for analysis. The Patent Office asserts that Smith *et al.* disclose the advantages of using MS over NMR analysis. The Patent Office further asserts that Ehring *et al.* disclose using similar MS analysis coupling with hydrogen/deuterium exchange method to study protein interaction for important biological/physiological functions and processes, *e.g.*, ligand bound to the protein, such as insulin-like growth factor I and its binding protein. Accordingly, the Patent Office asserts that it would have been obvious to one of skill in the art at the time the invention was made to have motivated Rogona *et al.* to adopt MS analysis as taught by

Smith et al. to study protein/ligand interaction as taught by Ehring *et al.* with reasonable expectation of success.

After careful review of the instant rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the references themselves to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. Manual of Patent Examining Procedures (MPEP) 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Independent claim 23 has been amended herein to recite a method of detecting a binding event involving a test protein with a test ligand, the method comprising, *inter alia*, providing an unpurified test protein. Support for the amendment to claim 23 can be found throughout the specification as filed, including particularly page 15, lines 2-7; page 24, lines 25-32; and page 57, line 16, through page 58, line 24. No new matter has been added. Applicants respectfully submit that neither Rogona *et al.* nor Smith *et al.* nor Ehring *et al.*, either alone or in combination, teach or suggest a method of detecting a binding event by providing an unpurified test protein.

The Patent Office asserts that Rogona *et al.* teach a method of studying protein stability and the use of buffer solution containing hydrogen/deuterium exchange method and varying denaturant in NMR to quantitatively study the protein stability. As acknowledged by the Patent Office, Rogona *et al.* do not teach a binding event, or using mass spectrometry for analysis. Further, applicants respectfully submit that Rogona *et al.* do not teach a method of detecting a binding event involving an unpurified test protein under native conditions, *i.e.*, an unpurified test protein is provided for testing. In fact, the current state of the art does not permit accurate analysis of unpurified test proteins using NMR, as NMR analysis requires very pure samples for analysis. Thus, applicants respectfully submit that Rogona *et al.* do not teach or suggest each element of

independent claim 23. Applicants further submit that neither Smith *et al.* nor Ehring *et al.* provides for the deficiencies of Rogona *et al.*

The Patent Office asserts that Smith *et al.* teach using MS analysis coupling with hydrogen/deuterium exchange method to study protein folding and unfolding, and the advantages of using MS over NMR analysis. However, applicants respectfully submit that Smith *et al.* do not teach the use of unpurified protein in the disclosed methods. Rather, Smith *et al.* cites several examples that pertain to MS analysis of purified protein samples. Particularly, applicants point to pages 8-9 and Figure 4, wherein the structural heterogeneity of rabbit muscle aldolase dissolved in D_2O was studied. Applicants respectfully submit that the terminology "dissolved in D_2O" indicates that purified rabbit muscle aldolase was used in the assay, rather than crude unpurified extracts, as disclosed in the present application. In addition, Smith *et al.* recites that mass spectra were taken for particular segments of the rabbit muscle aldolase, namely residues 257-269, in order to determine folding patterns of the residues. Applicants respectfully submit that in order to isolate the particular residues of aldolase, purified aldolase was inherently used in the disclosed methodologies. Further, applicants point to pages 10-11 and Figure 5 of Smith *et al.*, wherein a protein fragmentation/MS approach was used to detect minor structural changes in oxidized and reduced forms of cytochrome c. Particularly, the deuterium levels in eight peptides spanning the entire 104-residue backbone of cytochrome c were determined for oxidized or reduced cytochrome c incubated in D_2O. Again, applicants respectfully submit that in order to isolate the 8 peptides of the entire 104 backbone for use in the disclosed methods, purified cytochrome c was inherently employed. Thus, applicants respectfully submit that Smith *et al.* do not teach or suggest the use of unpurified proteins in the disclosed MS methods.

The Patent Office further asserts that Ehring *et al.* teach using MS analysis coupling with hydrogen/deuterium exchange method to study protein interaction for biological and physiological functions and processes. However, applicants respectfully submit that Ehring *et al.* do not teach use of an unpurified test protein in the disclosed methods. In particular, Ehring *et al.* teach (page 253, column 2) that for the hydrogen/deuterium exchange reactions, IGF was provided in house and dissolved in 5mM TRIS/D_2O. Applicants

respectfully submit that the IGF was in purified form, and dissolved in buffer for use in the disclosed methods.

Thus, applicants respectfully submit that the cited documents do not teach or suggest, either alone or in combination, all of the elements of independent claim 23. As such, the combination of Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* does not support the instant rejection of independent claim 23.

Claims 24-36 and 38-40 ultimately depend from independent claim 23. Claim 23 is believed to be patentably distinguished over the cited combination for the reasons set forth herein above. Accordingly, claims 24-36 and 38-40 are also believed to be patentably distinguished over the cited combination in view of their dependency from claim 23.

Hence, applicants respectfully request that the instant rejection of claims 23-36 and 38-40 under 35 U.S.C. §103(a) be withdrawn at this time. A Notice of Allowance is also respectfully requested.

III.B. Response to the 35 U.S.C. §103(a) Rejection of Claim 37 Based on Rogona *et al.* in view of Smith *et al.* in Combination with Ehring *et al.* and further in view of Villaneuva *et al.*

Claim 37 presently stands rejected under 35 U.S.C. §103(a) as being unpatentable over Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* and further in view of Villaneuva *et al.* The Patent Office concedes that the combination of Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* does not teach using sinapinic acid for MALDI mass spectrometry. However, the Patent Office asserts that Villanueva *et al.* teach treating the mass matix material with sinapinic acid. Thus, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have provided Rogona *et al.*, Smith *et al.*, and Ehring *et al.* with the packing material for MALDI, such as sinapinic acids taught by Villaneuva *et al.*

After careful review of the instant rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Original claim 23 has been amended herein to recite a method of detecting a binding event employing a test protein that is unpurified. As disclosed in detail

hereinabove, applicants respectfully submit that none of Rogona *et al.*, Smith *et al.*, and Ehring *et al.*, either alone or in combination, teach or suggest methods for use with an unpurified test protein.

The Patent Office asserts that Villanueva *et al.* teach using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to monitor hydrogen exchange on entire proteins, and that Villanueva *et al.* teach using MALDI-TOF MS to check the folding state of a protein. However, applicants respectfully submit that Villanueva *et al.* do not teach methods of using an unpurified test protein. Rather, Villanueva *et al.* only consider using lyophilized and pure samples. (*See* Villanueva *et al.* at page 28, sections 2.3, 2.4, and 2.5.)

Therefore, the cited documents do not teach or suggest, either alone or in combination, all the elements of independent claim 23. Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* and further in view of Villanueva *et al.*, either alone or in combination, do not teach or suggest a method of detecting a binding event using an unpurified test protein. In fact, each reference in the cited combination specifically teach only the use of purified test proteins. Since all the features of amended claim 23 are neither taught nor suggested by Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* and further in view of Villanueva *et al.*, either alone or in combination, it is respectfully submitted that claim 23 is now in proper condition for allowance. Since claim 37 depends from claim 23 and Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* and further in view of Villanueva *et al.* do not teach or suggest all the elements of claim 23 for the reasons stated above, Rogona *et al.* in view of Smith *et al.* in combination with Ehring *et al.* and further in view of Villanueva *et al.* do not teach or suggest all the elements of claim 37 either.

Therefore, applicants respectfully request that the instant rejection of claim 37 under 35 U.S.C. §103(a) be withdrawn at this time. A Notice of Allowance is also respectfully requested.

IV. Discussion of the New Claims

New claims 125-127 have been added herein as indicated above.

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Claim 125 recites, *inter alia*, that the test mixture is contacted with an exchange buffer for a specified time of exchange (t), and that detection of a binding event is a function of both denaturant concentration and the specified time of exchange (t). Support for new claim 125 can be found throughout the specification as filed, particularly in equation (6) on page 25, line 18; equation 8 on page 27, line 6; page 27, lines 7-27; and in claim 1 as originally filed.

Claim 126 depends from claim 125 and recites that the test protein is unpurified. Support for new claim 126 can be found throughout the specification as filed, including particularly page 15, lines 2-7; page 42, lines 25-32; and throughout Section IX, page 57, line 16, through page 58, line 24.

Claim 127 depends from claim 125 and recites that detecting a binding event further comprises fitting data comprising a change in mass of the test protein as a function of denaturant concentration and the specified time of exchange (t) to the equation $C_{1/2}^{SUPREX} = C_{1/2}^{den} - (RT/m) \ln(<k_{int}>t/0.693 - 1)$. Support for new claim 127 can be found throughout the specification as filed, including particularly in equation (8) and page 27, lines 1-27.

No new matter has been added by the addition of new claims 125-127.

It is respectfully submitted that new claims 125-127 are allowable over the cited art of record. None of the cited art, either alone or in combination, teaches or suggests each and every element of new independent claim 125. Specifically, none of Rogona *et al.*, Smith *et al.*, Ehring *et al.*, or Villaneuva *et al.*, either alone or in combination, teach or suggest contacting a test mixture with an exchange buffer for a specified time of exchange (t) and then detecting a binding event as a function of both denaturant concentration and the specified time of exchange (t). Accordingly, claims 126-127 are also believed to be patentably distinguished over the cited combination in view of their dependency from claim 125.

CONCLUSIONS

In light of the above Remarks, it is respectfully submitted that the present application is now in a proper condition for allowance and such action is earnestly solicited. If any minor issues should remain outstanding after the Patent Examiner has had an opportunity

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to study the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney so that all such matters may be resolved and the application be placed in a condition for allowance without the necessity for issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this Amendment to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 05/08/2006 By: _____

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